Congenital Etiologies:
(Part 1)

SOLUTION·S
www.solution-s.ca

Genetics 101

Terry Broda
NP-PHC, CDDN
Liz Kacew
NP-PHC, MScN

2015-January-14

Congenital Etiologies

SOLUTION·S

Every year, dozens of new genetic etiologies are identified that can cause developmental disabilities.

- In 1996, Opitz et al. (1996) reported more than 750 different etiologies that caused developmental disabilities (DD)
- These genetic disorders caused 33% - 50 % of DD!

Congenital Etiologies

SOLUTION·S

Definitions

Congenital Anomaly : present at birth may be genetic, infectious or environmental in origin, most often it is difficult to identify the exact causes

Genetic condition: result of the dysfunction of one or several genes

Hereditary Illness: Genetic disorder

*Not necessarily contradictory: certain genetic conditions are congenital & others are not (cancer), certain genetic conditions are hereditary (FXS) & others are not (DS, etc.)

Source: http://www.orpha.net/orphaschool/formations/transmission/ExternData/InfoTransmission-Dreamweaver/Transmission.pdf

Congenital Etiologies

SOLUTION·S

Grouped into 3 categories:

1. **Monogenetic disorder**: one gene (can be present on one or both chromosomes) cystic fibrosis, Tay-Sachs disease, sickle cell disease
2. **Multifactorial inherited disorder**: combo of small inherited variations i.e.: diabetes
3. **Chromosome disorder**: excess or deficiency of gene located on chromosome i.e.: DS, Fragile x, Prader Willi

Congenital Etiologies

SOLUTION·S

Risk Factors:

- Genetics
- Maternal infection: TORCH
- Environmental exposure: Alcohol, pesticides
- Maternal nutritional status: Phenylalanine, Folic acid

Congenital Etiologies

SOLUTION·S

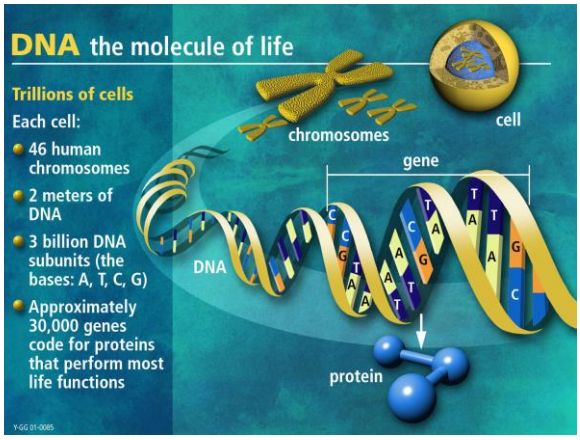
Examples:

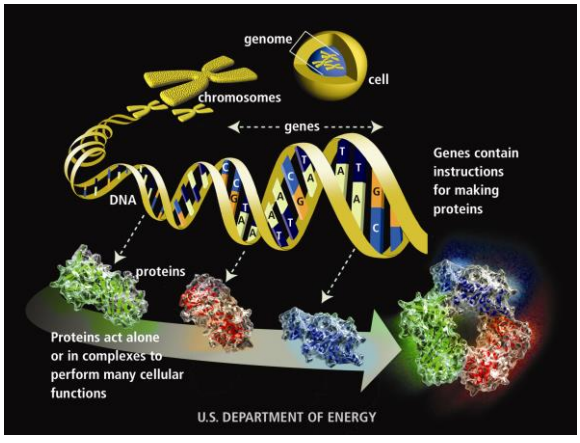
Phenylketonuria- **mutations** in the PAH gene cause PKU (low levels phenylalanine hydroxylase)

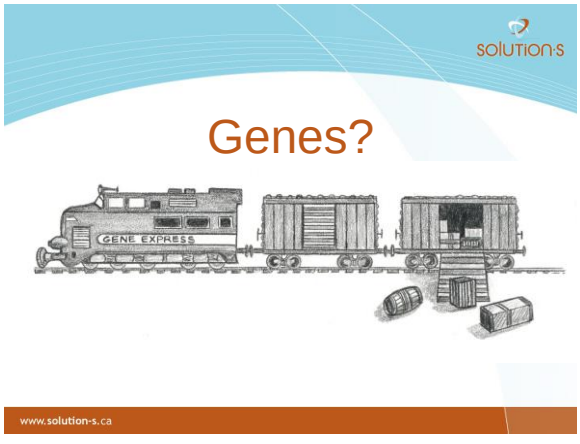
Velocardiofacial- missing segment in individuals with VCFS is 22q11.2.

Fragile X- caused by **mutation** in the FMR1 gene

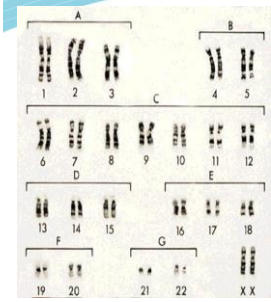
Cri du chat- 5p syndrome- **deletion** of p arm of chromosome 5


DNA the molecule of life
Trillions of cells
Each cell:
46 human chromosomes
2 meters of DNA
3 billion DNA subunits (the bases: A, T, C, G)
Approximately 30,000 genes code for proteins that perform most life functions
chromosomes
cell
gene
DNA
protein
Y-GG 01-0085


genome
cell
chromosomes
genes
DNA
Genes contain instructions for making proteins
proteins
Proteins act alone or in complexes to perform many cellular functions
U.S. DEPARTMENT OF ENERGY

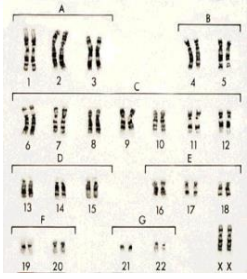

solution·s
Genes?
GENE EXPRESS
www.solution-s.ca

Chromosomes



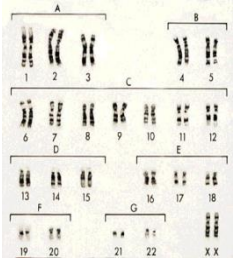
- 46 chromosomes organized in 23 pairs
- These chromosomes contain condensed coils of DNA code in the form of genes
- One member of each chromosome pair is inherited from your father & the other from your mother, at conception

Chromosomes



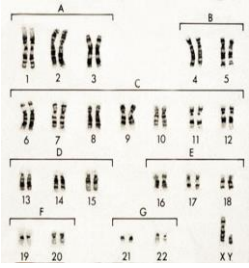
- 22 of the 23 pairs of chromosomes are similar in both sexes & are called **autosomes**
- The chromosomes making up the 23rd pair are called the **sex chromosomes** because they determine a person's gender

Chromosomes



- In females, both sex chromosomes are alike & are called chromosome X

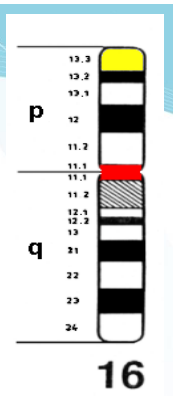
Chromosomes



- Whereas, males have one chromosome X & one chromosome Y
- Therefore, it is the male's spermatozoa that ultimately determines the sex of the fetus

Chromosomes

- Each chromosome has a centromere
- Shorter section above the centromere is called the « p » arm
  (« p » for petite)
- Longer section below centromere is known as the « q » arm
  (« q » for queue)
- A numeric system identifies all regions along both arms of each chromosome



Congenital Etiologies

http://www.patient.co.uk/doctor/**cri-du-chat-syndrome-pro**

Congenital Etiologies

SOLUTION·S

Grouped into 3 categories:

1. **Monogenetic disorder**: one gene (can be present on one or both chromosomes) cystic fibrosis, Tay-Sachs disease, sickle cell disease
2. **Multifactorial inherited disorder**: combo of small inherited variations i.e.: diabetes
3. **Chromosome disorder**: excess or deficiency of gene located on chromosome i.e.: DS, Fragile-X, Prader Willi

Congenital Etiologies

SOLUTION·S

MONOGENIC DISORDER:

- Mutations in a **single gene** - the Cystic Fibrosis Transmembrane Regulator (CFTR) gene - causes CF
- To develop CF, a child must inherit a defective **gene from both parents**
- If both parents are carriers, there is a 25 percent chance that each child they conceive will have CF, and a 50 percent chance that the child will be a carrier

Congenital Etiologies

SOLUTION·S

MULTIFACTORIAL INHERITED:

- Breast Cancer- BRCA1 or BRCA2 mutation have a 50 percent chance of inheriting the gene mutation

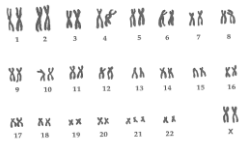
Congenital Etiologies

solution·s

Chromosomal Disorders

FIGURE 2.10 : Caryotype d'un sujet atteint du syndrome de Down*

Cette illustration des chromosomes d'une fillette affectée de trisomie 21 (photos du bas, figure 2.9) montre les trois chromosomes présents à la 21e paire.



* Figure élaborée à partir de STRICKBERGER, M.W. (1985) *Genetics*, 3e éd., New York, MacMillan, p. 424, figure 21-20.

Most frequent cause = Aneuploidy : an abnormal number of chromosomes (+ or -)

- Monosomy (more rare; ex. : Turner syndrome (45X0))
- Trisomies (ex. : Down, 13, 18, Klinefelter (XXY))

www.solution-s.ca

Down Syndrome

Discovered & described in 1866 by Langdon Down

www.solution-s.ca

solution·s

www.solution-s.ca

Congenital Etiologies

HOW:

3 genetic ways:

- 95% have trisomy 21 (an extra chromosome 21 in all their cells),
- 3-4% have a translocation form of the extra chromosome (where the extra chromosome 21 is attached to one of a different chromosome pair)
- about 1-2% are mosaic (only some cells are trisomic, the rest are normal)

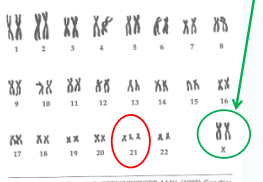
DS: Trisomy

- Trisomy 21: three copies of chromosome 21 instead of two copies (one from each parent).

FIGURE 2.10 : Caryotype d'un sujet atteint du syndrome de Down*

Cette illustration des chromosomes trisomie 21 (photos du bas, figure 2.9) montre les trois chromosomes présents à la 21e paire.

Is this a boy or a girl?



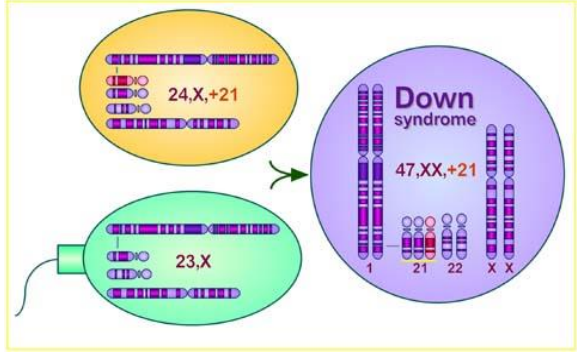
* Figure élaborée à partir de STRICKBERGER, M.W. (1985) *Genetics*, 3e éd., New York, MacMillan, p. 424, figure 21-20.

Video

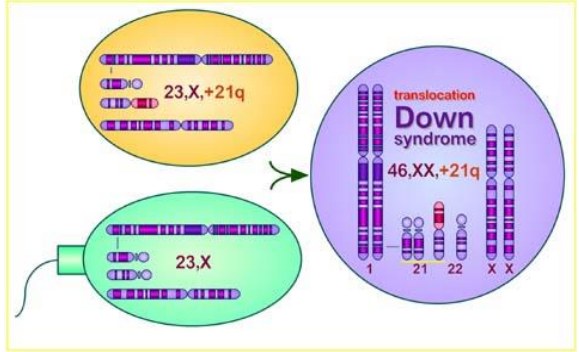
Your Genes, Your Health:

http://www.ygyh.org/

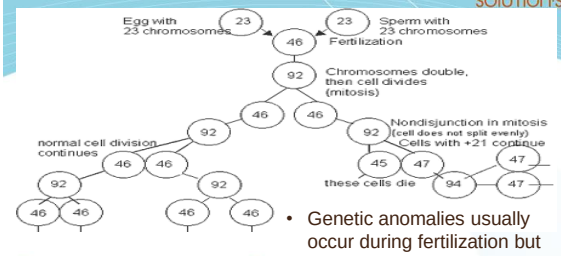
DS : Trisomy

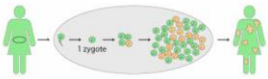


DS : Translocation



DS: Mosaic





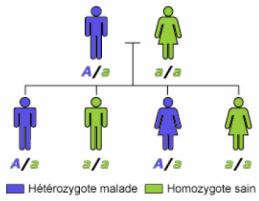
- Genetic anomalies usually occur during fertilization but when this occurs later on during cell division=> MOSAIC
- Persons w/ MDS present milder symptoms usually

www.solution-s.ca

Chromosomal disorders

- Women over 35 years of age present a much higher risk of having a child with a chromosomal disorder
- A karyotype can diagnose this condition

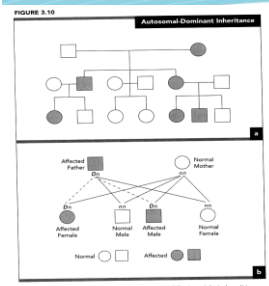
Mendelian Disorder– Autosomal dominant



A chaque grossesse,
le risque que l'enfant soit malade est de 50%

- The presence of a mutation on just one of the two copies of a gene is enough to develop the pathology (ex. Huntington)
- The prevalence is equivalent in males & females

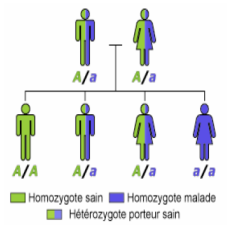
Mendelian Disorder– Autosomal dominant



(a) Autosomal-dominant family pedigree. (b) In autosomal-dominant inherited conditions, an affected person has a single, dominant (D) gene that causes the condition. With each pregnancy, he or she has a 50% chance of passing on the dominant gene for the condition and a 50% chance of passing on the normal (N) gene, which would not cause the condition to be present.

- The child that inherits the genetic mutation will develop the pathology
- The child that does not inherit the genetic mutation cannot transmit it to future generations
- Be watchful of the advancing age of the FATHER

Mendelian Disorder– Autosomal Recessive

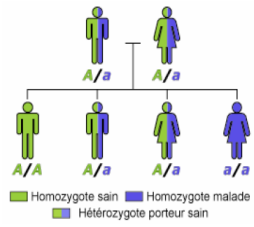


- BOTH parents must be carriers of the mutation
- This disorder may increase in frequency in certain ethnic groups
- (ex.PKU)

A chaque grossesse, le risque que l'enfant soit malade est de 25%

www.solution-s.ca

Mendelian Disorder– Autosomal Recessive

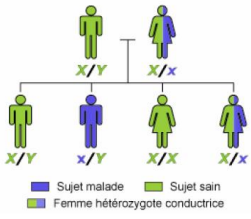


- The carrier does not necessarily have to have the condition. However, when 2 carriers have the same mutation & they reproduce, their offspring may have a :
  - 50% chance to be a carrier of the mutation without the disorder
  - 25% chance to not be a carrier nor to be afflicted with the disease

A chaque grossesse, le risque que l'enfant soit malade est de 25%

www.solution-s.ca

Mendelian Disorder– Recessive χ transmission



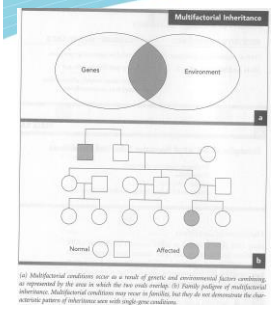
A chaque grossesse, le risque :
- qu'un garçon soit malade est de 50%
- qu'une fille soit conductrice est de 50%

(ex. Fragile χ, Lesch-Nyhan, Hunter)

- Mutation on chromosome χ
- A female carrier has a 50% chance of transmitting the pathological mutation of the gene to her son (who would be affected) & her daughter (who would be either a carrier or affected, but to a lesser degree)
- Males are more affected as they do not have an extra X chromosome
- This condition explains in part why there are more males with I/DD

www.solution-s.ca

Multifactorial disorders



(a) Multifactorial conditions occur as a result of genetic and environmental factors combining, as represented by the area in which the two ovals overlap. (b) Family pedigree of multifactorial inheritance. Multifactorial conditions may recur in families, but they do not demonstrate the characteristic pattern of inheritance seen with single-gene conditions.

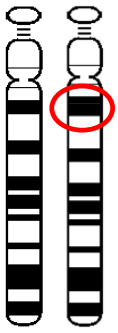
- Multifactorial causes
- A genetic predisposition that develops in certain environmental conditions
- For example : cancer, heart disease, spina bifida...

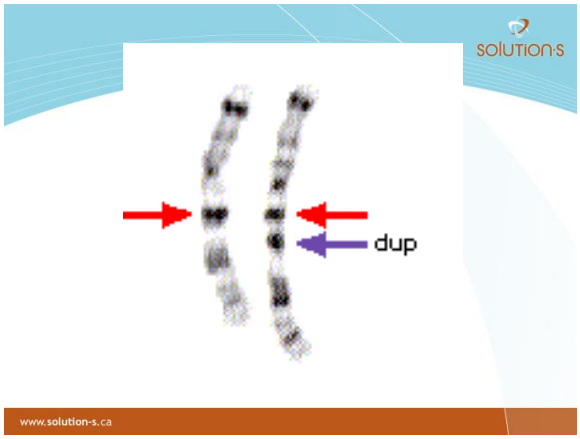
HEREDITY

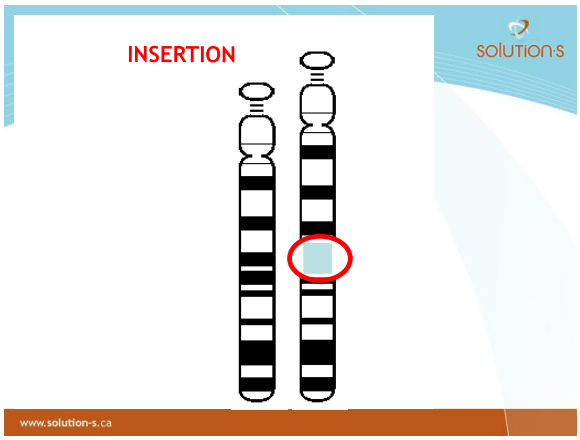
Video: NF2

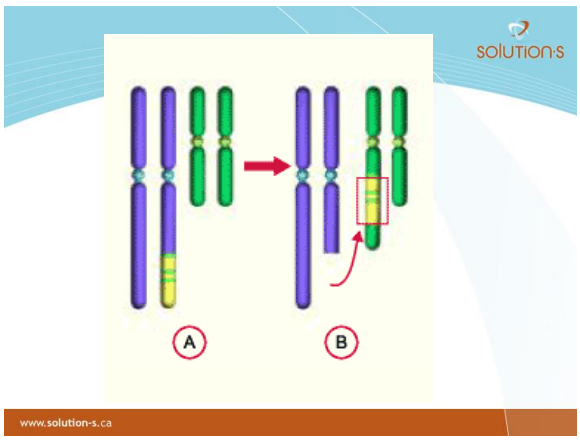
- http://www.ygyh.org/nf/inherited.htm

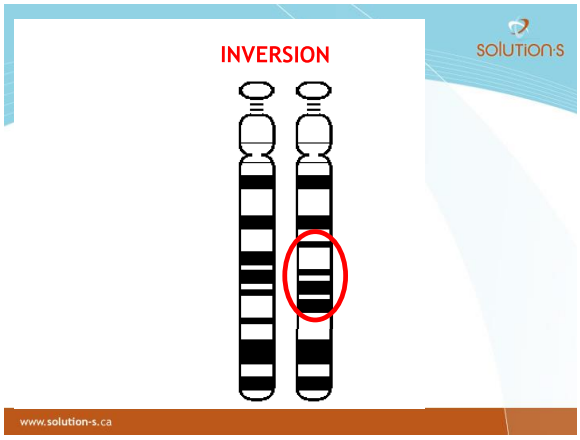
DUPLICATION

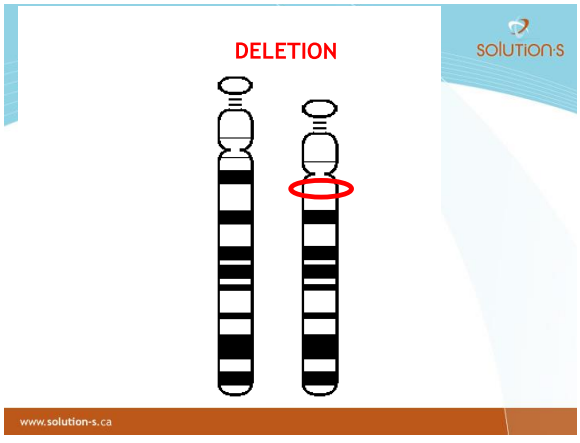


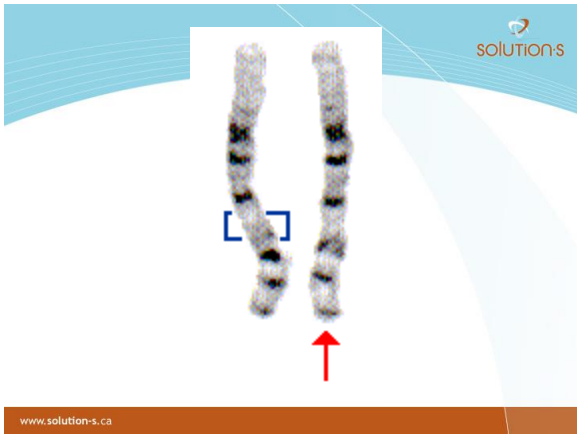

SOLUTION·S
dup
www.solution-s.ca


INSERTION
SOLUTION·S
www.solution-s.ca

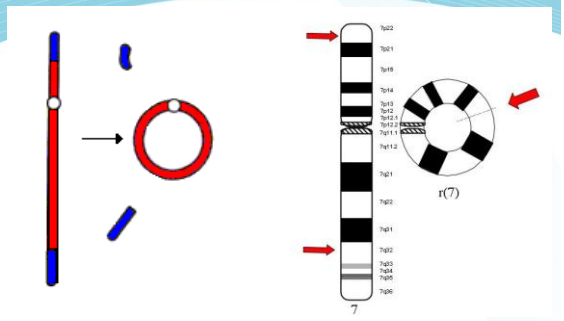

SOLUTION·S
A
B
www.solution-s.ca


INVERSION
SOLUTION·S
www.solution-s.ca

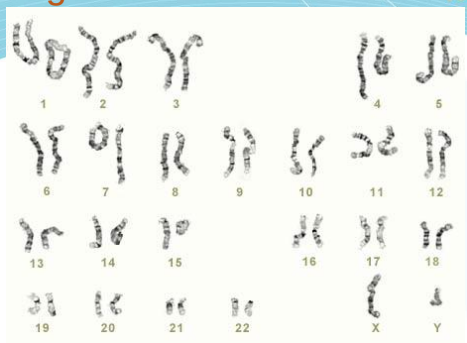

DELETION
SOLUTION·S
www.solution-s.ca


SOLUTION·S
www.solution-s.ca

Ring Chromosome



Ring Chromosomes



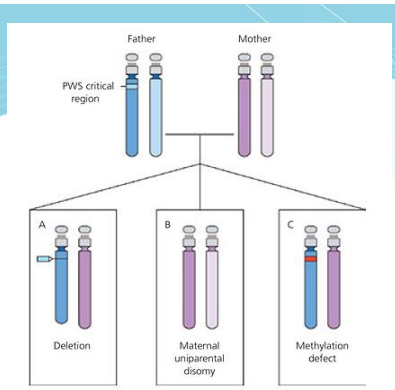
The Concept of Parental Imprinting

The expression of the pathological condition will depend on whether the pathological gene comes from the mother or the father.

Ex. : Prader-Willi Syndrome
or Angelman Syndrome

Prader Willi Syndrome is caused by a microdeletion on the chromosome 15, that is inherited from the father (or more rarely when there are two copies of the gene from the mother)

Angelman Syndrome is caused by a microdeletion of the exact same region of chromosome 15, however, this mutation is inherited from the mother (or more rarely, when there are 2 copies from the father)



Genetic Tests

1) Karyotype

2) FISH test

Definition of Karyotype

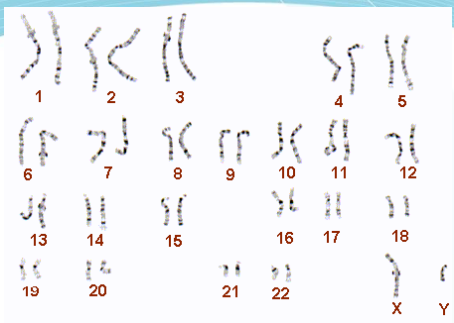
The American Heritage® Medical Dictionary :

1. The characterization of the chromosomal complement of an individual or a species, including number, form, and size of the chromosomes

2. A photomicrograph of chromosomes arranged accor ding to a standard classification

Genetic tests: The Karyotype

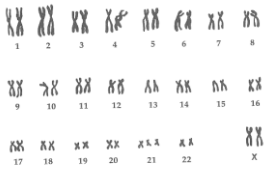
The Karyotype



Genetic tests (cont.)

FIGURE 2.10 : Caryotype d'un sujet atteint du syndrome de Down*

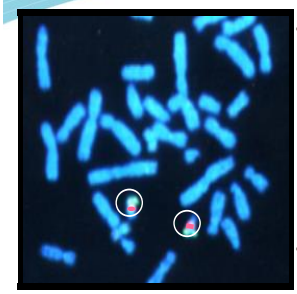
Cette illustration des chromosomes d'une fillette affectée de trisomie 21 (photos du bas, figure 2.9) montre les trois chromosomes présents à la 21e paire.



* Figure élaborée à partir de STRICKBERGER, M.W. (1985) *Genetics*, 3e éd., New York, MacMillan, p. 424, figure 21-20.

- The karyotype can identify cytogenetic abnormalities
- Since 1960, we have been able to use karyotyping to diagnose several genetic syndromes (Down, Klinefelter, …)

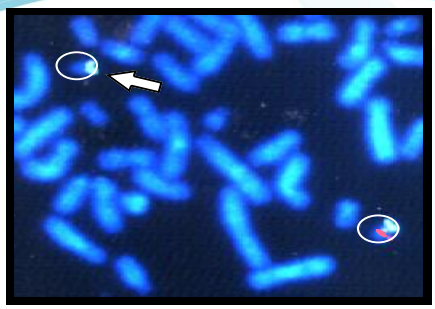
FISH=Fluorescent In Situ Hybridization



- A specific molecular probe, labelled with a bright fluorescent chemical marker is added to a chromosome preparation to find its sequence-specific match at the molecular level
- Useful in the diagnosis of deletion syndromes

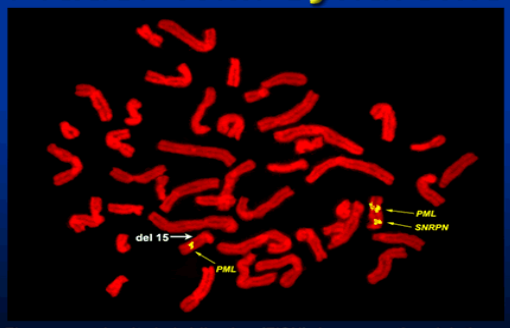
www.solution-s.ca

Results of the FISH test for Velocardiofacial Syndrome (*22q-*)



www.solution-s.ca

Prader-Willi Syndrome



Fluorescent *in situ* hybridization (FISH) demonstrating deletion (del) of *SNRPN* probe on one of the chromosomes 15s.

www.solution-s.ca

Figure 1

GENOTYPE & PHENOTYPE

solution-s

- 1972 : William Nyhan proposed for the first time the notion of a **behavioral phenotype**
- **Definition (Dykens, 1995):**

  The heightened probability or likelihood that people with a given syndrome will exhibit certain behavioral & developmental sequelae relative to those without the syndrome

GENOTYPE & PHENOTYPE

solution-s

- **Phenotype** = The observable manifestations of a person's genotype (which includes physical characteristics such as height & facial features, as well as predisposition to certain health problems: heart disease, strabismus)
- **Genotype =** A person's genetic makeup (the combination of genes of an organism or an individual)

Dykens, Hodapp & Finucane, 2000

Particular Profiles Genetics 101

solution-s

- **Physical** Phenotype
- **Behavioral** Phenotype
- **Medical** Phenotype
- **Cognitive** Phenotype

GENETICS 101

Figure 1.19 Prader-Willi-like phenotype in a boy with fragile X syndrome.

Which syndrome comes to mind?

GENETICS 101

- BEWARE OF HASTY GENERALISATIONS :
- *Important variations - medically, physically, cognitively & behaviorally- are observed in individuals with the SAME genetic syndrome*

Why should you test?

- Medical & psychiatric comorbidities
- Behavioral strategies
- Educational strategies
- Psychosocial considerations
- Parental closure
- Interventions to prevent further complications
- Future genetic risks in families

How using a genetic approach can help you to better understand I/DD

solution·s

- **A** : Genetic etiology
- **B** : Particular profile for each of the syndromes: medically, physically, cognitively & behaviorally
- **A + B** = better adapted interventions
- In certain cases, early identification can even prevent the development of deficits (ex. : phenylketonuria, PKU)

www.solution-s.ca

solution·s

THANK YOU!

www.solution-s.ca

solution·s

29-2450 Lancaster
Ottawa, Ontario K1B 5N3
T 613 249-8593
F 613 249-0198
info@solution-s.ca
www.solution-s.ca